Neurological Deterioration Under Isovolemic Hemodilution With Hydroxyethyl Starch in Acute Cerebral Ischemia

Henning Mast, MD and Peter Marx, MD

In a prospective study, we randomly allocated 70 patients with acute ischemic stroke to two therapy groups. Up to interim analysis, 33 patients underwent bloodletting, with simultaneous infusion of an identical volume of hydroxyethyl starch (10%, 200/0.5). The target hematocrit was 35%. A control group of 37 patients did not receive hemodilution. Apart from an unequal sex distribution, the two groups were comparable with regard to age, cardiovascular risk factors, and medical history. In the hemodilution group, the mean hematocrit fell from 44.4% to 37.7%. After 14 days, improvement on the neurological score scale was 3.3 points in the hemodilution group compared with 6.5 points in the control group (p=0.12). Subgroups with early inclusion (<12 hours) or pronounced lowering of hematocrit (>15% of initial hematocrit) also did not profit from hemodilution. Clinical deterioration observed in eight hemodilution group patients (p<0.01) led to discontinuation of the study for ethical reasons. (Stroke 1991;22:680–683)

Despite numerous experimental and clinical investigations, hemodilution therapy remains controversial in patients with acute ischemic stroke. Apart from the first Scandinavian trial,1 neither previous nor subsequent studies were able to substantiate a relevant improvement of neurological deficit or mortality. The Scandinavian multicenter trial2–4 even showed an increased mortality in patients with "deep infarctions,"4 and the Hemodilution in Stroke Study Group5 ended its investigation of hypervolemic hemodilution with pentastarch because of excess mortality in the treatment group.

The present study was started as a prospectively randomized investigation of the effect of isovolemic hemodilution with hydroxyethyl starch (10%, 200/0.5) in 200 patients with acute ischemic stroke. Hydroxyethyl starch appears to be superior to dextran from a hemorheological point of view. Although both are comparable in their effect on whole-blood viscosity, hydroxyethyl starch also lowers plasma viscosity and has fewer side effects than dextran.

Subjects and Methods

We included 70 patients from consecutive admissions to the Steglitz University Hospital over a 1-year period if their acute neurological symptoms had begun within 48 hours before admission and if they presented a neurological deficit. A cerebral computed tomogram verified the diagnosis of ischemia. Exclusion criteria included patients with hematocrit values of more than 50% on admission, anticoagulation on admission, clinically manifest myocardial insufficiency, myocardial infarction in the last 4 weeks, angina pectoris, renal insufficiency (serum creatinine greater than 200 μmol/L), coma or severe second diseases such as cancer. Before inclusion in the study, patients were informed verbally and gave written consent to participate. In aphasic patients, the declaration of consent was made by relatives. This procedure was approved by the Ethics Committee of the Steglitz University Hospital.

After randomization, 33 patients allocated to the hemodilution group (H group) underwent bloodletting (500 ml for hematocrit greater than 40%; 300 ml for hematocrit less than 40%), and infusion of an identical volume of hydroxyethyl starch (10%, 200/0.5) was begun simultaneously. Hydroxyethyl starch, 100–200 ml, was infused within 15 minutes and the remainder over 3–5 hours.

If the target hematocrit of 35% could not be attained with a single dilution, the procedure was repeated on the following day. Hemodilution was not carried out in the control group (C group, 37 patients). All other therapeutic measures, including 250 mg aspirin/day and adequate fluid intake, were identical in both groups.
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we applied the neurological score scale already used the clinical course. This score (best performance, 48 in the Scandinavian multicenter study 2-4 to evaluate there were no relevant differences with regard to patients (Table 1: H group, n=27; C group, n=29),
evaluated with the scale used. In the remaining 56 basilar artery thrombosis were excluded. One pa-
tient in the H group and five in the C group were
excluded because their deficits (somatosensory def-
cit or homonymous hemianopia) could not be

There were no statistically significant differences between the two patient groups with regard to age, cardiovascular risk factors, or relevant previous dis-
eas. The male/female ratio was 15/18 and 26/11 in the H and C groups, respectively (p<0.05).
A total of 14 patients was excluded for secondary analysis. In three H group patients, hemodilution
was terminated because of contraindications, such as gastrointestinal hemorrhage, electrophysi-
ographic signs of ischemia, and renal insufficiency. In two other H group patients, anticoagulation for
cerebral artery thrombosis was considered necessary and replaced hemodilution. In the C group, one
patient with hemispheric hemorrhage and two with cerebral artery thrombosis were excluded. One
patient in the H group and five in the C group were excluded because their deficits (somatosensory de-
cit or homonymous hemianopia) could not be
evaluated with the scale used. In the remaining 56 patients (Table 1: H group, n=27; C group, n=29),
there were no relevant differences with regard to age, prior diseases, cardiovascular risk factors, time
of inclusion, initial neurological score, or initial hematocrit, but sex distribution still differed  signif-
ificantly. Table 1 shows the almost equal distribution of initial neurological scores in both groups.

On the day of admission and on day 2, 3, 7, and 14, we applied the neurological score scale already used in the Scandinavian multicenter study2-4 to evaluate the clinical course. This score (best performance, 48 points) mainly appraises motor performance. Blood
pressure and heart rate were measured before and after hemodilution, as well as routinely once a day.

Blood samples for rheological analysis were obtained by venipuncture. Hematocrit was determined by cen-
trifugation at 15,000g over 5 minutes. Additional pa-
rameters, such as whole-blood viscosity and plasma viscosity, erythrocyte aggregation, and filterability, will be published separately.

All results are given as mean values with 95% confidence intervals. Statistical significance was tested with Fisher's exact test, χ², and Student's t test. Because it became necessary to exclude patients retrospectively, we carried out both an intention-to-
treat and secondary analysis.

Results

The mean hematocrit on admission was 44.5% (42.7-46.2%) in the C group and 44.4% (42.8-46.0%) in the H group. In the H group, it was lowered to 37.7% (36.3-39.1%) 3-5 hours after the beginning of therapy. Further dilutions were necessary on the second day in 20 patients and on the third day in 16 patients. Hematocrit reduction persisted up to the 14th day.

Mean arterial blood pressure on admission was 109 and 107 mm Hg in the H and C groups, respectively. We found a slight reduction in both groups (103 and 104 mm Hg, respectively) after 3 days; heart rates of 79 and 76 beats/min, respectively, remained essen-
tially unchanged during the treatment period. There were no allergic complications of therapy.

After 2 weeks, the average improvement in neuro-
logical score was 3.3±0.4 in the H group and 6.5±0.7 points in the C group (p=0.12). The neurological score of six hemodiluted patients (eight patients in the intention-to-treat analysis) had deteriorated as compared with the finding on admission. By contrast, clinical deteriorations were not registered in the C group (Table 2). This result was significant for both the

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**Table 1. Patient Data at Randomization in Secondary Analysis**

<table>
<thead>
<tr>
<th>Hemodilution group (n=27)</th>
<th>Control group (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 (62-72)</td>
</tr>
<tr>
<td>Range (yrs)</td>
<td>36-92</td>
</tr>
<tr>
<td>Male/female*</td>
<td>11/16</td>
</tr>
<tr>
<td>Time after stroke onset (hrs)</td>
<td>23 (18-28)</td>
</tr>
<tr>
<td>Early inclusion (&lt;12 hrs)</td>
<td>8/27</td>
</tr>
<tr>
<td>Neurological score (points)</td>
<td>29.7</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.4 (42.8-46.0)</td>
</tr>
</tbody>
</table>

Previous medical history (n[%])

- Transient ischemic attack | 0 (0) | 3 (10)
- Stroke | 4 (15) | 6 (21)
- Myocardial infarction | 6 (22) | 4 (14)
- Myocardial insufficiency | 5 (19) | 2 (7)
- Atrial fibrillation | 3 (11) | 3 (10)
- Angina pectoris | 4 (15) | 2 (7)
- Hypertension | 7 (26) | 11 (38)
- Diabetes mellitus | 9 (33) | 9 (31)
- Hyperlipidemia | 3 (11) | 4 (14)

Values are mean and 95% confidence interval (in parentheses) where applicable.

*Significant difference (p<0.05) between hemodilution and control groups.

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**FIGURE 1. Score clusters of hemodilution and control groups on admission. Data from secondary analysis; scores divided into quartils.**

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intention-to-treat and the secondary analysis groups ($p<0.01$). Worsening occurred in two cases during the first hemodilution, and four patients (six in the intention-to-treat analysis) deteriorated on the following days without hemodilution. Table 3 provides details of the patients with clinical deterioration.

There was one death, a patient in the H group who had been excluded from secondary analysis because anticoagulation was considered necessary. The initial hematocrit had no influence on clinical outcome. However, five of the deteriorating patients were diluted by more than 15% of baseline hematocrit.

Eight patients in the H group had been included within 12 hours after the ischemic event. Of these, three deteriorated, and five improved or remained unchanged. Of the remaining 19 patients who were hemodiluted after more than 12 hours, three deteriorated, and 16 improved or remained unchanged (data from secondary analysis). Thus, there was a trend to a poorer result with early beginning of hemodilution. Because of these clinical results, the study was discontinued for ethical reasons.

**Discussion**

The results of published studies on the clinical effectiveness of isovolemic hemodilution in human patients are contradictory. The first Scandinavian trial showed a statistically significant benefit in the hemodilution group, but this could not be confirmed in the following multicenter study. Its sole significant result was an increased mortality in patients with "deep infarctions" after hemodilution. The large Italian investigation also was unable to document a positive effect, although all patients had been treated within 12 hours after the ischemic event.

These investigations used low molecular weight dextrans in aliquot amounts as a substitute for the blood volume removed. Because of the water-binding capacity of dextran, the resulting hemodilution is not strictly isovolemic in terms of intravascular volume, but slightly hypervolemic. The same applies to the exchange with hydroxyethyl starch in the study presented here, even though the volume effect of this plasma expander is less.

The results of this study showed significant clinical deterioration in the hemodiluted group only. Because most deterioration occurred on the second or third day without hemodilution, it is unlikely that it was related to immediate hypovolemia during the blood and hydroxyethyl starch exchange procedure. Heart rate, blood pressure, and hematocrit follow-ups do not support the assumption of delayed hypovolemia as a cause of deterioration.

The argument that an increase of heart minute volume is essential to achieve a beneficial clinical effect of hemodilution was considered by the Hemodilution in Stroke Study Group, which used pentastarch for hypervolemic hemodilution. Raised mortality among hemodiluted patients led to early discontinuation of this trial. Cause of early death was cerebral edema, whereas mortality after the seventh day was due to renal failure, myocardial infarction, and new stroke, all of which could have been caused by the therapy. Trends to clinical improvement in subgroups were due to a harvesting effect (dead patients were excluded from further analysis) and differ from our findings.

The disappointing results of most clinical studies are in contrast to experiments showing smaller infarct areas in hemodiluted animals compared with controls. One difference between these experiments and the clinical situation is that hemodilution in animal models was carried out either during or immediately after vessel ligation, whereas under clinical conditions, hemodilution usually starts after a delay of several hours when irreversible tissue damage is likely to have already occurred.

### Table 2. Neurological Outcome (Day 1–14)

<table>
<thead>
<tr>
<th>Hemodilution group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Improved/unchanged</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>6 (8)*</td>
</tr>
</tbody>
</table>

Data from secondary and intention-to-treat (in parentheses) analyses. Statistically significant ($p<0.01$, Fisher's exact test) difference between H and C groups.

### Table 3. Data From Secondary Analysis of Six Deteriorating Patients in Hemodilution Group

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Score (day 1/14)</th>
<th>Hematocrit (%)</th>
<th>Inclusion time (hrs)</th>
<th>CCT</th>
<th>Cardiovascular risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>70/F</td>
<td>10/8</td>
<td>45/35</td>
<td>24</td>
<td>Deep infarct MCA</td>
<td>None</td>
</tr>
<tr>
<td>62/F</td>
<td>10/24</td>
<td>50/37</td>
<td>7</td>
<td>Deep infarct MCA</td>
<td>None</td>
</tr>
<tr>
<td>72/F</td>
<td>41/27</td>
<td>40/33</td>
<td>20</td>
<td>Lacune MCA</td>
<td>None</td>
</tr>
<tr>
<td>67/F</td>
<td>22/9</td>
<td>46/38</td>
<td>4</td>
<td>Deep infarct MCA</td>
<td>None</td>
</tr>
<tr>
<td>60/F</td>
<td>27/22</td>
<td>47/40</td>
<td>47</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>92/F</td>
<td>35/30</td>
<td>43/36</td>
<td>12</td>
<td>Cortical infarct MCA</td>
<td>MI, AF, MI-INSUF</td>
</tr>
<tr>
<td>Mean</td>
<td>69.7</td>
<td>46/36</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCT, cranial computerized tomography; MCA, middle cerebral artery; MI, myocardial infarction; AF, atrial fibrillation; MI-INSUF, myocardial insufficiency.
In addition, hemodilution in animal experiments usually is carried out under constant orthostatic conditions and with maintenance of a constant blood pressure, which cannot be ensured in the clinical situation. This may explain why cerebral oxygen deficiency does not develop even at very low hematocrit values, whereas reduction of the autoregulation reserve caused by hemodilution might not be compensated by patients.

The increase of cerebral blood flow during hemodilution merely compensates for the reduction in oxygen capacity. It does not allow inferences to be made with regard to clinical efficacy. An optimal hematocrit of approximately 45% was calculated from cerebral blood flow measurements at various hematocrit values in humans and is likely to be even higher for ischemic tissue because the vasodilation reserve is already reduced, if not exhausted.

This compares well with the results of the Scandinavian multicenter study, in which the mortality of ischemic stroke was lowest for patients with a hematocrit of approximately 45%.

We conclude that both isovolemic and hypervolemic hemodilution below a hematocrit of approximately 45% is a potentially dangerous stroke therapy for which a clear clinical advantage has not been documented up to now. Hypervolemic hemodilution in particular carries a high risk in multimorbid patients.

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References


KEY WORDS • cerebral ischemia • hematocrit • hemodilution
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